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L7: Entry 227 of 631 File: USPT Dec 11, 2001

DOCUMENT-IDENTIFIER: US 6329389 B1
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TITLE: Amine compounds, their production and use

Brief Summary Text (6):
Somatostatin is known to inhibit production and/or secretion of various hormones, growth factors, and physiologically active substances. As the hormones inhibited by somatostatin, mentioned are growth hormone (GH), thyroid-stimulating hormones (TSH), prolactin, insulin, and glucagon. Therefore, somatostatin has various functions in endocrine systems, exocrine systems and nerve systems, and drugs targeting somatostatin are being developed (e.g., Endocrinology, vol.136, p.3695-3697, 1995; Trends in Pharmacological Sciences, pp.87-94, vol.18, 1997).

Brief Summary Text (7):
Diseases caused by somatostatin include life-style related diseases such as diabetes; central nervous system diseases, immune system diseases, and hormone-dependent tumors. Trials to develop somatostatin itself or somatostatin analogues as a drug have been conducted. For instance, octreotide known as a somatostatin receptor agonist has been marketed as a drug for treating hormone-dependent tumors.

Brief Summary Text (137):
(22) a pharmaceutical composition of the above (21) which is a somatostatin receptor agonist;

Brief Summary Text (138):
(23) a pharmaceutical composition of the above (21) which is a somatostatin receptor antagonist;

Brief Summary Text (561):
The "hormones" include, for example, growth hormone (GH), growth hormone-releasing hormones (GHRH), thyroid stimulating hormone(TSH), prolactin, insulin, glucagon, etc. The "growth factors" include, for example, insulin-like growth factor-i (IGF-1) and vascular endothelial cell growth factor (VEGF). The "physiologically active substances" include, for example, vasoactive intestinal polypeptide (VIP), gastrin, glucagon-like peptide-1, amylin, substance-P, CCK(cholecystokinin), amylase, interleukins such as interleukin-1 (IL-1) and etc., cytokines such as TNF-.alpha. and etc., cardiotropin, etc.

Brief Summary Text (563):
Compounds (I) and (I') are useful (1) for drugs for treatment of tumors such as acromegaly, TSH-producing tumors, nonsecretory (afunctional) hypophysial tumors, ectopic ACTH (adrenocorticotrophic hormone)-producing tumors, medullar thyroid carcinoma, VIP-producing tumors, glucagon-producing tumors, gastrin-producing tumors, insulinoma and carotinoid tumor, (2) for drugs for treatment of insulin-dependent and non-insulin dependent diabetes mellitus or a variety of diseases associated with them, namely diabetic complications such as diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, Doan syndrome and orthostatic hypotension, (3) for drugs for improvement of hyperinsulinemia or for treatment of obesity caused by inhibition of appetite, and overeating, (4) for drugs for treatment of acute pancreatitis, chronic pancreatitis, pancreal/intestinal fistula, hemorrhagic ulcer, peptic ulcer, gastritis, hyperchylia, regurgitant esophagitis, (5) for drugs for improvement of various symptoms associated with the

Helicobacter pylori infection, for example, inhibitors of gastrin hypersecretion, (6) for drugs for inhibition of amylase secretion associated with endoscopic cholangiopancreatography, and drugs for prognostic treatment of surgical operation of pancreas, (7) for drugs for treatment of diarrhea due to intestinal malabsorption, promotion of secretion or dyskinesia of the digestive tracts (for example, short bowel syndrome), diarrhea due to the drugs for cancer chemotherapy, diarrhea due to congenital small intestine atrophy, diarrhea due to neuroendocrine tumors such as VIP-producing tumors, diarrhea due to AIDS, diarrhea due to graft versus host reaction associated with bone marrow transplantation, diarrhea due to diabetes mellitus, diarrhea due to celiac plexus blocking, diarrhea due to systemic sclerosis and diarrhea due to eosinophilia, (8) for drugs for treatment of dumping syndrome, irritable colitis, Crohn disease and inflammatory bowel disease, (9) for drugs for treatment of tumors or cancers (e.g., thyroid cancer, large bowel cancer, breast cancer, prostatic cancer, small cell lung cancer, non-small cell cancer, pancreatic cancer, stomach cancer, cholangiocarcinoma, hepatic cancer, vesical cancer, ovarian cancer, melanoma, osteosarcoma, chondrosarcoma, malignant pheochromocytoma, neuro-blastoma, brain tumors, thymoma, renal cancers), leukemia (e.g., leukemia of basophilic leukemia, chronic lymphocytic leukemia, chronic myeloid leukemia, Hodgkin disease, and non-Hodgkin lymphoma) (drugs for treatment of these cancers can be used for monotherapy or concomitant therapy with other anticancer drugs such as Tamoxifen, LHRH agonists, LHRH antagonists, interferon-.alpha., .beta. and .gamma., interleukin-2 and etc,), (10) for drugs for prevention and treatment of hypertrophic cardiomyopathy, arteriosclerosis, valvular disease, myocardiac infarction (especially, myocardiac infarction post percutaneous transluminal coronary arterioplasty) and reangioplasty, (11) for drugs for treatment of hemorrhage of esophageal varicosis, cirrhosis and peripheral blood vessel disorders, (12) for drugs for treatment of diseases associated with general or local inflammation, for example, polyarteritis, rheumatoid arthritis, psoriasis, sunburn, eczema and allergy (e.g., asthma, atopic dermatitis and allergic rhinitis) because they inhibit or modulate the secretion of physiologically active substances acting on the immune system (e.g., Substance P, tachykinin and cytokines), (13) for drugs for treatment of dementia (e.g., Alzheimer disease, Alzheimer-type senile dementia, vascular/multi-infarct dementia), schizophrenia, epilepsy, depression, generalized anxiety disorder, sleep disorder, and multiple sclerosis, because they give influence on the production and secretion of nerve regulators, (14) for drugs for treatment of oculopathy (e.g., glaucoma, etc.), (15) for drugs for prevention and treatment of acute bacterial meningitis, acute virus encephalitis, adult respiratory distress syndrome, bacterial pneumonia, severe systemic mycotic infection, tuberculosis, spinal damage, bone fracture, hepatic failure, pneumonia, alcoholic hepatitis, virus A hepatitis, virus B hepatitis, virus C hepatitis, AIDS infection, human papilloma virus infection, influenza infection, metastasis of cancer, multiple myeloma, osteomalacia, osteoporosis, bone Paget disease, nephritis, renal failure, sepsis, septic shock, hypercalcemia, C: hypercholesterolemia, hypertriglyceridemia, hyperlipemia, systemic lupus erythematosus, transient ischemic attach and alcoholic hepatitis, (16) for cure of organ transplantation, burns, trauma, and alopecia, (17) as analgesics for chronic or acute pain (e.g., postoperative pain, inflammatory pain, dental pain, bone disease (e.g., arthritis, rheumatism, osteoporosis etc.) derived pain), (18) for imaging of tumors having somatostatin receptors after administering radioactive substance (e.g., .sup.123 I, .sup.125 I, .sup.111 In, etc.) to compound (I) or (I') either directly or via a suitable spacer, and (19) for targeting tumors with somatostatin receptors using compound (I) or (I') conjugated with anti-cancer drugs directly or using a suitable spacer.

Brief Summary Text (566):
The "prevention or treatment of diseases or symptoms caused by insufficiency of growth hormone or IGF-1" includes, for example, treatment of insulin-dependent and non-insulin dependent diabetes mellitus or a variety of diseases associated with them, namely diabetic complications such as diabetic retinopathy, diabetic nephropathy, diabetic neuropathy, Doan syndrome and orthostatic hypotension; prevention of adverse effects caused by disassimilation of glucocorticoid; prevention or treatment of osteoporosis; stimulation of immune system (e.g., promotion of increase in hemocytes such as lymphocyte; strengthening of an antimicrobial activity or an antiviral activity); promotion of cure of burns and trauma; acceleration in the treatment of bone fracture; treatment of acute or chronic renal diseases; treatment or improvement of diseases or symptoms (short

stature, delayed growth) associated with insufficiency of growth hormone in adults or infants; treatment of obesity; promotion of recovery after surgical operations; improvement of delayed growth associated with Prader-Willi syndrome and Turner's syndrome; treatment of delayed intrauterine growth and skeletogenous disorders; treatment of peripheral neuropathy; treatment of Noonan's syndrome, schizophrenia and depression; treatment or prevention of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease; treatment of pulmonary insufficiency and ventilation dependence; treatment of malabsorption syndrome; improvement of cachexia or protein loss caused by cancer or AIDS; promotion of weight increase and proteopexis in patients in the case of TPN (total parenteral nutrition); treatment of hyperinsulinemia; promotion of induction of ovulation; improvement of menopausal disorders; improvement of senile constitution. Further, the compound of the present invention is useful in mammals such as domestic animals for promotion of growth; increase in milk production; strengthening of an antimicrobial and antiviral activity by stimulation of immune system; stimulation in growth of wool in sheeps. In use for the above purposes, for example, in the treatment of osteoporosis, other drugs for treatment of osteoporosis (e.g., bisphosphonates, vitamin D preparations, calcitonin preparations, PTH preparations, Osten, etc.) can be used concomitantly. In the treatment of diabetes mellitus or diseases associated with them, other antidiabetic agents (e.g., thiazolidinediones such as Troglitazone, pioglitazone, Rosiglitazone, and etc.; glucagon antagonists; glucose absorption inhibitors such as acarbose, and etc) can be used concomitantly. Further, r other hormones promoting growth hormone secretion (e.g., GHRH), GH or IGF-1 can be used concomitantly. In improvement of menopausal disorders, a hormone supplemental therapy (e.g., therapy by estrogen preparations, Raloxifene, Tamoxifen) can be used concomitantly. In the case in which stimulation of immune system is intended, cytokines or cytokine activity enhancing agents can be used concomitantly.

CLAIMS:

20. A pharmaceutical composition of claim 19 wherein the somatostatin receptor binding inhibitor is a somatostatin receptor agonist.

21. A pharmaceutical composition of claim 19 wherein the somatostatin receptor binding inhibitor is a somatostatin receptor antagonist.

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DOCUMENT-IDENTIFIER: US 6329197 B1
TITLE: DNA encoding galanin GALR3 receptors and uses thereof

Brief Summary Text (2):
The neuropeptide galanin and its receptors hold great promise as targets for the development of novel therapeutic agents. Galanin is widely distributed throughout the peripheral and central nervous systems and is associated with the regulation of processes such as somatosensory transmission, smooth muscle contractility, hormone release, and feeding (for review, see Bartfai et al., 1993). In the periphery galanin is found in the adrenal medulla, uterus, gastrointestinal tract, dorsal root ganglia (DRG), and sympathetic neurons. Galanin released from sympathetic nerve terminals in the pancreas is a potent regulator of insulin release in several species (Ahren and Lindskog, 1992; Boyle et al., 1994), suggesting a potential role for galanin in the etiology or treatment of diabetes. High levels of galanin are observed in human and rat anterior pituitary where galanin mRNA levels are potently upregulated by estrogen (Vrontakis et al., 1987; Kaplan et al., 1988). The presence of galanin in the hypothalamic-pituitary-adrenal axis coupled with its potent hormonal effects has led to the suggestion that galanin may play an integral role in the hormonal response to stress (Bartfai et al., 1993).

Brief Summary Text (4):
Galanin receptors elsewhere in the CNS may also serve as therapeutic targets. In the spinal cord galanin is released from the terminals of sensory neurons as well as spinal interneurons and appears to play a role in the regulation of pain threshold (Wiesenfeld-Hallin et al., 1992). Intrathecal galanin potentiates the anti-nociceptive effects of morphine in rats and produces analgesia when administered alone (Wiesenfeld-Hallin et al., 1993; Post et al., 1988); galanin receptor agonists may therefore be useful as analgesic agents in the spinal cord. Galanin may also play a role in the development of Alzheimer's disease. In the hippocampus galanin inhibits both the release (Fisone et al., 1987) and efficacy (Palazzi et al., 1988) of acetylcholine, causing an impairment of cognitive functions (Sundstrom et al., 1988). Autopsy samples from humans afflicted with Alzheimer's disease reveal a galaninergic hyperinnervation of the nucleus basalis (Chan-Palay, 1988), suggesting a role for galanin in the impaired cognition characterizing Alzheimer's disease. Together these data suggest that a galanin antagonist may be effective in ameliorating the symptoms of Alzheimer's disease (see Crawley, 1993). This hypothesis is supported by the report that intraventricular administration of the peptide galanin antagonist M35 improves cognitive performance in rats (Ogren et al., 1992). Human galanin receptors thus provide targets for therapeutic intervention in multiple CNS disorders.

Brief Summary Text (27):
This invention provides a process for determining whether a compound is a GALR3 receptor agonist which comprises contacting a cell transfected with and expressing DNA encoding the GALR3 receptor with the compound under conditions permitting the activation of the GALR3 receptor, and detecting an increase in GALR3 receptor activity, so as to thereby determine whether the compound is a GALR3 receptor agonist.

Brief Summary Text (28):
This invention provides a process for determining whether a compound is a GALR3 receptor antagonist which comprises contacting a cell transfected with and expressing DNA encoding the GALR3 receptor with the compound in the presence of a

known GALR3 receptor agonist, such as galanin, under conditions permitting the activation of the GALR3 receptor, and detecting a decrease in GALR3 receptor activity, so as to thereby determine whether the compound is a GALR3 receptor antagonist.

Brief Summary Text (32):
This invention provides a method of screening a plurality of chemical compounds not known to inhibit the activation of a GALR3 receptor to identify a compound which inhibits the activation of the GALR3 receptor, which comprises (a) preparing a cell extract from cells transfected with and expressing DNA encoding the GALR3 receptor, isolating a membrane fraction from the cell extract, contacting the membrane fraction with the plurality of compounds in the presence of a known GALR3 receptor agonist, under conditions permitting activation of the GALR3 receptor; (b) determining whether the activation of the GALR3 receptor is reduced in the presence of the plurality of compounds, relative to the activation of the GALR3 receptor in the absence of the plurality of compounds; and if so (c) separately determining the inhibition of activation of the GALR3 receptor for each compound included in the plurality of compounds, so as to thereby identify the compound which inhibits the activation of the GALR3 receptor.

Brief Summary Text (37):
This invention provides a method of modifying feeding behavior of a subject which comprises administering to the subject an amount of a compound which is a galanin receptor agonist or antagonist effective to increase or decrease the consumption of food by the subject so as to thereby modify feeding behavior of the subject. In an embodiment, the compound is a GALR3 receptor antagonist and the amount is effective to decrease the consumption of food by the subject. In another embodiment the compound is administered in combination with food.

Brief Summary Text (38):
In yet another embodiment the compound is a GALR3 receptor agonist and the amount is effective to increase the consumption of food by the subject. In a still further embodiment, the compound is administered in combination with food. In other embodiments the subject is a vertebrate, a mammal, a human or a canine.

Detailed Description Text (17):
G-protein coupled receptors such as the GALR3 receptors of the present invention are characterized by the ability of an agonist to promote the formation of a high-affinity ternary complex between the agonist, the receptor, and an intracellular G-protein. This complex is formed in the presence of physiological concentrations of GTP, and results in the dissociation of the alpha subunit of the G protein from the beta and gamma subunits of the G protein, which further results in a functional response, i.e., activation of downstream effectors such as adenylyl cyclase or phospholipase C. This high-affinity complex is transient even in the presence of GTP, so that if the complex is destablized, the affinity of the receptor for agonists is reduced. Thus, if a receptor is not optimally coupled to G protein under the conditions of an assay, an agonist will bind to the receptor with low affinity. In contrast, the affinity of the receptor for an antagonist is normally not significantly affected by the presence or absence of G protein. Functional assays may be used to determine whether a compound binds to the receptor, but may be more time-consuming or difficult to perform than a binding assay. Therefore, it may desirable to produce a receptor which will bind to agonists with high affinity in a binding assay. Examples of modified receptors which bind agonists with high affinity are disclosed in WO 96/14331, which describes neuropeptide Y receptors modified in the third intracellular domain. The modifications may include deletions of 6-13 amino acids in the third intracellular loop. Such deletions preferably end immediately before the polar or charged residue at the beginning of helix six. In an embodiment, the deleted amino acids are at the carboxy terminus of the third intracellular domain. Such modified receptors may be produced using methods well-known in the art such as site-directed mutagenesis or recombinant techniques using restriction enzymes.

Detailed Description Text (80):
This invention provides a process for determining whether a chemical compound is a GALR3 receptor agonist which comprises contacting cells transfected with and

expressing DNA encoding the GALR3 receptor with the compound under conditions permitting the activation of the GALR3 receptor, and detecting an increase in GALR3 receptor activity, so as to thereby determine whether the compound is a GALR3 receptor agonist.

Detailed Description Text (81):
This invention provides a process for determining whether a chemical compound is a GALR3 receptor agonist which comprises preparing a cell extract from cells transfected with and expressing DNA encoding the GALR3 receptor, isolating a membrane fraction from the cell extract, contacting the membrane fraction with the compound under conditions permitting the activation of the GALR3 receptor, and detecting an increase in GALR3 receptor activity, so as to thereby determine whether the compound is a GALR3 receptor agonist.

Detailed Description Text (83):
This invention provides a process for determining whether a chemical compound is a GALR3 receptor antagonist which comprises contacting cells transfected with and expressing DNA encoding the GALR3 receptor with the compound in the presence of a known GALR3 receptor agonist, such as galanin, under conditions permitting the activation of the GALR3 receptor, and detecting a decrease in GALR3 receptor activity, so as to thereby determine whether the compound is a GALR3 receptor antagonist.

Detailed Description Text (84):
This invention provides a process for determining whether a chemical compound is a GALR3 receptor antagonist which comprises preparing a cell extract from cells transfected with and expressing DNA encoding the GALR3 receptor, isolating a membrane fraction from the cell extract, contacting the membrane fraction with the ligand in the presence of a known GALR3 receptor agonist, such as galanin, under conditions permitting the activation of the GALR3 receptor, and detecting a decrease in GALR3 receptor activity, so as to thereby determine whether the compound is a GALR3 receptor antagonist.

Detailed Description Text (91):
This invention provides a pharmaceutical composition which comprises an amount of a GALR3 receptor agonist determined by the above-described processes effective to increase activity of a GALR3 receptor and a pharmaceutically acceptable carrier. In an embodiment, the GALR3 receptor agonist is not previously known.

Detailed Description Text (92):
This invention provides a pharmaceutical composition which comprises an amount of a GALR3 receptor antagonist determined by the above-described processes effective to reduce activity of a GALR3 receptor and a pharmaceutically acceptable carrier. In an embodiment, the GALR3 receptor antagonist is not previously known.

Detailed Description Text (93):
This invention provides a pharmaceutical composition which comprises an amount of a GALR3 receptor agonist effective to increase activity of a GALR3 receptor and a pharmaceutically acceptable carrier.

Detailed Description Text (94):
This invention provides a pharmaceutical composition which comprises an amount of a GALR3 receptor antagonist effective to reduce activity of a GALR3 receptor and a pharmaceutically acceptable carrier.

Detailed Description Text (115):
This invention provides a pharmaceutical composition which comprises an amount of a GALR3 receptor agonist determined by any of the above processes effective to increase activity of a GALR3 receptor and a pharmaceutically acceptable carrier. In an embodiment, the GALR3 receptor agonist is not previously known.

Detailed Description Text (116):
This invention provides a pharmaceutical composition which comprises an amount of a GALR3 receptor antagonist determined by any of the above processes effective to reduce activity of a GALR3 receptor and a pharmaceutically acceptable carrier. In an

embodiment, the GALR3 receptor antagonist is not previously known.

Detailed Description Text (124):
This invention provides a method of screening a plurality of chemical compounds not known to inhibit the activation of a GALR3 receptor to identify a compound which inhibits the activation of the GALR3 receptor, which comprises (a) contacting cells transfected with and expressing the GALR3 receptor with the plurality of compounds in the presence of a known GALR3 receptor agonist, under conditions permitting activation of the GALR3 receptor; (b) determining whether the activation of the GALR3 receptor is reduced in the presence of the plurality of compounds, relative to the activation of the GALR3 receptor in the absence of the plurality of compounds; and if so (c) separately determining the inhibition of activation of the GALR3 receptor for each compound included in the plurality of compounds, so as to thereby identify the compound which inhibits the activation of the GALR3 receptor.

Detailed Description Text (125):
This invention provides a method of screening a plurality of chemical compounds not known to inhibit the activation of a GALR3 receptor to identify a compound which inhibits the activation of the GALR3 receptor, which comprises (a) preparing a cell extract from cells transfected with and expressing DNA encoding the GALR3 receptor, isolating a membrane fraction from the cell extract, contacting the membrane fraction with the plurality of compounds in the presence of a known GALR3 receptor agonist, under conditions permitting activation of the GALR3 receptor; (b) determining whether the activation of the GALR3 receptor is reduced in the presence of the plurality of compounds, relative to the activation of the GALR3 receptor in the absence of the plurality of compounds; and if so (c) separately determining the inhibition of activation of the GALR3 receptor for each compound included in the plurality of compounds, so as to thereby identify the compound which inhibits the activation of the GALR3 receptor.

Detailed Description Text (128):
In an embodiment of the above processes, the cells are transfected with and expressing GIRK1 and GIRK4. In an embodiment of the above processes, receptor activation is determined by measurement of potassium channel activation. In an embodiment, receptor activation is determined by measurement of an increase in inward potassium current. In another embodiment, inhibition of receptor activation is determined by a smaller increase in inward potassium current in the presence of the compound and a galanin receptor agonist than in the presence of only the galanin receptor agonist. In an embodiment, the galanin receptor agonist is galanin.

Detailed Description Text (134):
This invention provides a process for determining whether a compound selectively inhibits the activation of the GALR3 receptor relative to another galanin receptor, which comprises: (a) determining the decrease in the potency of a known galanin receptor agonist for the GALR3 receptor in the presence of the compound, relative to the potency of the agonist in the absence of the compound; (b) determining the decrease in the potency of the agonist for such other galanin receptor in the presence of the compound, relative to the potency of the agonist in the absence of the compound; and (c) comparing the decrease in potencies so determined, the presence of a greater decrease in potency for the GALR3 receptor than for such other galanin receptor indicating that the compound selectively inhibits the activation of the GALR3 receptor. In an embodiment of the above processes, such other galanin receptor is a GALR1 receptor. In another embodiment, such other galanin receptor is a GALR2 receptor.

Detailed Description Text (142):
This invention provides a GALR3 receptor agonist detected by the above-described methods. This invention provides a GALR3 receptor antagonist detected by the above-described methods. In an embodiment the cell is a non-mammalian cell, for example, a Xenopus oocyte or melanophore. In another embodiment the cell is a neuronal cell, for example, a glial cell line such as C6. In an embodiment, the cell is non-neuronal in origin. In a further embodiment, the cell is a Cos-7 or a CHO cell, a 293 human embryonic kidney cell, an LM(tk-) cell or an NIH-3T3 cell.

Detailed Description Text (165):

This invention provides a method of modifying feeding behavior of a subject which comprises administering to the subject an amount of a compound which is a galanin receptor agonist or antagonist effective to increase or decrease the consumption of food by the subject so as to thereby modify feeding behavior of the subject. In one embodiment, the compound is a GALR3 receptor antagonist and the amount is effective to decrease the consumption of food by the subject. In another embodiment the compound is administered in combination with food.

Detailed Description Text (166):
In yet another embodiment the compound is a GALR3 receptor agonist and the amount is effective to increase the consumption of food by the subject. In a still further embodiment, the compound is administered in combination with food. In other embodiments the subject is a vertebrate, a mammal, a human or a canine.

Detailed Description Text (168):
This invention provides a method of treating Alzheimer's disease in a subject which comprises administering to the subject an amount of a compound which is a galanin receptor antagonist effective to treat the subject's Alzheimer's disease. In one embodiment, the galanin receptor antagonist is a GALR3 receptor antagonist and the amount of the compound is effective to treat the subject's Alzheimer's disease.

Detailed Description Text (169):
This invention provides a method of producing analgesia in a subject which comprises administering to the subject an amount of a compound which is a galanin receptor agonist effective to produce analgesia in the subject. In another embodiment, the galanin receptor agonist is a GAUR3 receptor agonist and the amount of the compound is effective to produce analgesia in the subject.

Detailed Description Text (170):
This invention provides a method of decreasing nociception in a subject which comprises administering to the subject an amount of a compound which is a GALR3 receptor agonist effective to decrease nociception in the subject.

Detailed Description Text (171):
This invention provides a method of treating pain in a subject which comprises administering to the subject an amount of a compound which is a GALR3 receptor agonist effective to treat pain in the subject.

Detailed Description Text (172):
This invention provides a method of treating diabetes in a subject which comprises administering to the subject an amount of a compound which is a GALR3 receptor antagonist effective to treat diabetes in the subject.

Detailed Description Text (173):
This invention provides a method of decreasing feeding behavior of a subject which comprises administering a compound which is a GALR3 receptor antagonist and a compound which is a Y5 receptor antagonist, the amount of such antagonists being effective to decrease the feeding behavior of the subject. In an embodiment, the GALR3 antagonist and the Y5 antagonist are administered in combination. In another embodiment, the GALR3 antagonist and the Y5 antagonist are administered once. In another embodiment, the GALR3 antagonist and the Y5 antagonist are administered separately. In still another embodiment, the GALR3 antagonist and the Y5 antagonist are administered once. In another embodiment, the galanin receptor antagonist is administered for about 1 week to 2 weeks. In another embodiment, the Y5 receptor antagonist is administered for about 1 week to 2 weeks.

Detailed Description Text (174):
In yet another embodiment, the GALR3 antagonist and the Y5 antagonist are administered alternately. In another embodiment, the GALR3 antagonist and the Y5 antagonist are administered repeatedly. In a still further embodiment, the galanin receptor antagonist is administered for about 1 week to 2 weeks. In another embodiment, the Y5 receptor antagonist is administered for about 1 week to 2 weeks. This invention also provides a method as described above, wherein the compound is administered in a pharmaceutical composition comprising a sustained release formulation.

Detailed Description Text (320):
The effects of galanin, galanin derivatives, and related peptides and compounds may be evaluated by intracerebroventricular (i.c.v.) injection of the peptide or compound followed by measurement of food intake in the animal. Measurement of food intake was performed for hours after injection, but other protocols may also be used. Saline was injected as a control, but it is understood that other vehicles may be required as controls for some peptides and compounds. In order to determine whether a compound is a GALR3 antagonist, food intake in rats may be stimulated by administration of (for example) a galanin receptor agonist through an intracerebroventricular (i.c.v.) cannula. A preferred anatomic location for injection is the hypothalamus, in particular, the paraventricular nucleus. Methods of cannulation and food intake measurements are well-known in the art, as are i.c.v. modes of administration (Kyrkouli et al., 1990, Ogren et al., 1992). To determine whether a compound reduces agonist-stimulated food intake, the compound may be administered either simultaneously with the peptide, or separately, either through cannula, or by subcutaneous, intramuscular, or intraperitoneal injection, or more preferably, orally.

Detailed Description Text (359):
A series of galanin and galanin-related peptides were tested at the human GALR3 receptor for agonist and antagonist activities. Of these peptides, porcine galanin, human galanin, M32, C7, M35, M15 (spantide), galanin -7-29, galanin 1-16, and M40 evoked agonist activity at a fixed dose of 1 .mu.M. D-Trp2-galanin and galanin 3-29 were inactive. EC.sub.50 s were constructed from cumulative concentration-response measurements performed on a series of oocytes (FIGS. 6B, 8). EC.sub.50 s (in rank order) for M32, porcine galanin, C7, galanin -7-29, galanin 1-16 and M40 were 44.5, 222, 343, 1906, 2030, and 2265 nM, respectively (Table 6). This rank order of potency was similar to that observed for K.sub.i values in binding assays using the rat GalR3 receptor in COS-7 cells with the exception of galanin -7-29, which had an affinity between galanin and M32 in the binding assay.

Detailed Description Text (368):
The physiological and anatomical distribution of galanin-containing neurons suggests potential roles of galanin receptors mediating effects on cognition, analgesia, neuroendocrine regulation, control of insulin release and control of feeding behavior. Of particular relevance to the role of the novel GALR3 receptor, are those functions mediated by galanin receptors in the rat hypothalamus.

Detailed Description Text (370):
Peptide displacement assays indicate that the rat GALR3 receptor has a unique pharmacological profile. The low affinity for M40, in particular, invites further speculation as to the physiological role of the rat GALR3 receptor. It is noted that M40 was reported to be inactive, for example, when tested for antagonism of galaninergic inhibition of glucose-stimulated insulin release in rat pancreas, (Bartfai, 1993). In another example, intrathecal M40 was a weak antagonist of the galanin-facilitated flexor reflex in rat (Xu, 1995). It was observed in feeding assays that M40 was less potent but as effective as galanin in stimulating food intake when injected icv into rat brain. The data are consistent with a role for the GALR3 receptor in a range of physiologic and pathophysiologic functions including diabetes, pain, obesity and eating disorders, and furthermore suggest that the rat GALR3 receptor may represent a target for the design of therapeutic compounds. The cloning of the rat GALR3 receptor further enables the design and development of in vitro functional assays to determine the agonist or antagonist properties of peptides and drug development candidates.

Other Reference Publication (30):
Selve, et al., "Galanin receptor antagonists attenuate spinal antinociceptive effects of DAMGO, tramadol and non-opioid drugs in rats" Brain Res. (1996) 734(2): 177-187.